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|---|---|
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16

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/853,188 | ABULJADAYEL, ILHAM MOHAMED SALEH SAEED | |
| | Examiner | Art Unit | |
| | Karen A. Canella | 1643 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 1-100 is/are pending in the application.

4a) Of the above claim(s) 42-100 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-41 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date Feb 11, 2004.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Acknowledgement is made of applicant's election with traverse of Group I, drawn to a device for forming or increasing the relative number of undifferentiated cell in a cell population. The traversal is on the grounds that the restriction is improper because it separates the subject matter of Groups I and II and applicant argues that the search for the subject matter of Group II will include the subject matter of Group I. This has been considered but not found persuasive. The groups are drawn to a method an apparatus. The search for the apparatus can be made be made without the search for the method because the intended use of the apparatus, i.e. in carrying our the method of Group II, does not affect the patentability of said apparatus. Applicant further argues that the invention must be independent and distinct in order for the restriction to be proper. This has been considered but not found persuasive. As s et forth in the restriction requirement of June 3, 2003, the device of Group I can be used in a method of preparing a transformed cell line. Applicant argues that this is not materially different from preparing a retrodifferentiated cell. This is not persuasive, because transformed cell lines are well-known in the art, and a process of preparing a retrodifferentiated cell is not known in the art. Further, the method of Group II can be practiced "by hand" by using conventional small-scale tissue culture techniques and without requiring the device of Group I. Thus, the restriction requirement is deemed proper and adhered to. The restriction requirement is therefore made final.

The election of species requirement set forth in sections 8 and 9 of the paper mailed June 3, 2005, is withdrawn.

2. Claims 1-100 are pending. Claims 42-100, drawn to non-elected inventions, are withdrawn from consideration. Claims 1-41 are examined on the merits.

### *Priority*

3. Acknowledgement is made to claim to an earlier effective filing date through 09/568,254, filed May 10, 2000 and UK applications 0101315.0, filed January 18, 2001 and 0107093.7, filed March 21, 2001. After review of each of these applications, it is noted that the 09/568,254 application does not make mention of the instant device, and therefore lacks adequate written

description of the claimed invention. Accordingly the instant invention will be given priority only to UK application 0101315.0, filed January 18, 2001.

### *Claim Objections*

4. Claims 4, 6, 8, 10, 12, 14, 16 and 18 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 3, 5, 7, 9, 11, 13, 15 and 17, respectively. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

### *Claim Rejections - 35 USC § 101*

5. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims 1-40 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility, for the same reasons of record which were set forth in the parent application of 09/568,254. All references in this section provided in parent application 09/568,254.

The instant claims are drawn to a device which includes retrodifferentiation means capable of causing a committed cell to "retrodifferentiate" into an undifferentiated cell. The specification sets forth a method of preparing a hematopoietic stem cell comprising contacting a B-cell or a CFC-B cell with an agent that causes said cell to "retro-differentiate" into hematopoietic stem cell. The specification states that the resulting mixture is altered and expressing various cluster of differentiation markers commensurate with the presence of T-cells. The specification reports that analysis of the DNA taken from the mixture indicates that germline restriction patterns of the V(D)J region was "restored" after treatment of an enriched mixture of mature B-cells with the CR3/43 antibody, and that the alteration of the hematopoietic markers were evidence of "retro-differentiation of mature B-cells to hematopoietic stem cells which then

had the capability to differentiate into cells of another lineage, namely T-cells. Based on this evidence the specification thus concludes that the binding of the CR3/43 antibody to the HLA-DR receptor induced "retro-differentiation" of mature B-cells into hematopoietic stem cells that differentiated into cells of another lineage, namely T-cells. The specification puts forth experimental data wherein lymphocytic preparations consisting of either enriched B-cells (at least 70%), or whole blood taken from leukemia patients containing 73-95% B-cells are reacted with the antibody CR3/43. This antibody is known to bind to the homologous region of the beta chain of HLA-DR, a class I MHC molecule. The mixture is incubated for 24 hours, in which time lymphocytic preparations containing the antibody (vs control samples which do not contain the antibody) aggregated and deposited a monolayer of adherent cells in the bottom of the test tube (pg. 36, lines 12-14). Analysis of the mixture with panels of antibodies to various cluster of differentiation markers revealed that the phenotype of the mixture was now altered with respect to the starting mixture. Further, the specification makes claim to the "re-insertion" of the circular DNA fragment which is generated during DH to JH recombination in immature B-cells and known not to be replicated with the genomic DNA (Fits and Mage, Eur J Immunology, 1995, vol. 25, pp. 700, 2nd column). The specification fails to demonstrate that attachment of the CR3/43 antibody or any other antibody which binds to the homologous beta region of HLA-DR to a single mature B-cell expressing cluster of differentiation markers consistent with mature B-cells, such as CD21 and Cdw75, alters the pattern of gene expression from mature B-cell to hematopoietic stem cell with concomitant loss of mature B-cell markers and concomitant gain of germline restriction patterns in the genomic DNA. The specification does not describe a highly purified collection of lymphocytes which would be free of hematopoietic precursor cells, thus the data put forth in the specification can be interpreted to arise from a mixture of mature lymphocytes and hematopoietic precursor cells of more than one lineage as a source of mature differentiated cells having cluster of differentiation markers not evident in the starting mixture, followed by maturation of the hematopoietic precursor cells to exhibit said markers which were not evident in the starting mixture. The experiments described by the specification are essentially the same as those originally used to obtain lymphoblastoid cell lines as described by Freshney (see Freshney, I., Culture of Animal Cells: A Manual of Basic Technique, 3rd edition, 1994, p. 345) whereby said cell line was obtained by the high density culturing of peripheral

lymphocytes from blood at greater than 106 cells/ml, (the specification describes the culture density to be optimally at 2 X 107cells/ml) to obtain a cell pellet followed by a monolayer of adherent cells attached to the culture tube from the cell pellet. The eventual shedding of cells into suspension was indicative that progenitor cells had adapted to proliferate under the culture conditions and subculturing of the growing cells into cell lines could then commence. The specification indicates that samples which did not form aggregates (samples which were not treated with the CR3/43 antibody) did not exhibit "retro-differentiation". The specification thus concludes that the presence of the CR3/43 antibody bound to the HLA-DR receptor induced "retro-differentiation" of mature B-cells into hematopoietic stem cells that differentiated into cells of another lineage, namely T-cells. Further, it is known in the art that the circular DNA fragment produced from rearrangement is not retained in the cell (Fitz and Mage, European Journal of Immunology, 1995, Vol. 25, page 700, cited in a previous Office action). Further, current experiments by Rolink et al (Cold Spring Harbor Symposia on Quantitative Biology, 1999, Vol. 64, pp. 21-25) demonstrate that a pro-B cell blocked from differentiating into a pre-B cell could develop myeloid characteristics. However, the resulting myeloid cells preserved the DHJH/DHJH rearranged pattern and did not revert into the original germline pattern (Rolink et al, page 24, column 1, last paragraph). This is evidence that the cells which have allegedly "reincorporated" the germline DNA extruded by the rearrangement of the DHJH genes have not originated from cells which have undergone said rearrangement. The specification provides no reasonable explanation for why the circular DNA fragment, which is germ-line in origin, and known to be eliminated from the more differentiated cell is suddenly "re-acquired" by the said "retro-differentiated cells". the most plausible explanation is that its reappearance is the result of the repopulation of the sample by a stem cell not eliminated by the monoclonal antibody.

The examiner contends that the binding of the CR3/43 antibody to the hematopoietic cells of the sample induced selective apoptosis in the committed cells. The evidence for this phenomenon is set forth in

A. Pettersen et al, (Journal of Immunology, 1998, vol. 160, pp. 4343-4352), who teach that binding of monoclonal antibodies to HLA-A2 class I alpha-2 domain induces apoptotic cell death (abstract),

B. Genestier et al (Blood, 1997, Vol. 90, pp. 3626-3639) and Genestier et al (Blood, 1997, Vol. 90, pp. 726-735) who teach that two monoclonal antibodies which bind to an epitope of the alpha-1 domain induces apoptotic cell death of activated, but not resting peripheral T-lymphocytes (abstract), and B-cells (abstract), respectively.

C. Woodle et al, (Journal of Immunology, 1997, vol. 158, pp. 2156-2164) who teach that an antibody which recognizes the alpha-3 domain induces apoptosis in T-cells (abstract),

D. Vidovic and Toral (Cancer Letter, 1998, Vol. 128, pp. 127-135) teach that incubation of monoclonal antibody which binds to HLA-DR of tumor B-cells induced apoptosis selectively in malignant B-cells (abstract, and page 130, second column, first and second full paragraphs).

E. Thibeault et al (Cellular Immunology, 1999, Vol. 192, pp. 79-85) teach that binding of antibodies to HLA-DR on monocytes induces apoptotic monocyte death (abstract).

F. Berto et al (Journal of Immunology, 2000, vol. 164, pp. 2379-2385) teach that binding of monoclonal antibodies to HLA-DR of mature dendritic cells of monocytic origin led to marked apoptosis in said mature cells but significantly less apoptosis was observed in immature dendritic cells (abstract, and page 2380, second column, under the heading "Detection of HLA-DR induced cell death").

G. the abstract of Tawara et al (Blood, 2001, vol. 98, pp. 250-B) which teaches that HLA-Dr monoclonal antibodies induce apoptosis in B-cell lymphomas.

It appears that the preponderance of data supports the induction of apoptosis upon binding of antibodies to the HLA receptor. It is further concluded from the work of Berto et al that this induction of apoptosis is favored in more mature cells, which explain the observation set forth in the instant specificati0n, that the phenotype of the samples had changed after addition of the monoclonal antibody. One of skill in the art would conclude that in light of the above publications, selective apoptosis was induced in the non-stem cell portion of the sample, and that repopulation of the sample took place in vitro by the stem cells remaining in the mixture.

### *Claim Rejections - 35 USC § 112*

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-40 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 9 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "miniaturized" in claims 9 and 10 is a relative term which renders the claim indefinite. The term "miniaturized" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. For purpose of examination the term miniaturized will not limit the maximum size of the coulter counter.

11. Claims 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 9 and 10 require a "miniaturized" coulter counter. The specification does not provide a written description of said miniaturized coulter counter, and because of the lack of a limiting definition in the specification to define the metes and bounds of miniaturized, the genus of "miniaturized coulter counter" includes coulter counters which differ substantially in structural features from conventional coulter counters. Thus, the contemplation of a miniaturized

coulter counter in the disclosure fails to adequately describe the genus of coulter counters included as part of the claimed device.

***Claim Rejections - 35 USC § 102***

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1-4 and 15-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Gruenberg (U.S. 5,627,070).

Claims 1 and 2 are drawn to a device comprising a chamber, means for introducing into said chamber a population of cells including committed cells, means for introducing into said chamber "retrodifferentiation means", and incubation means. Claims 3 and 4 embody the device of claim 1 wherein said device comprises a measuring means for measuring the volume of the cell population and/or , means for conducting cell counts and for measuring the cell concentration of said cell population and/or, transfer means for transferring an amount of cell population from a storage container into a chamber and/or transfer means for transferring a volume of agent to be added to the chamber, and/or transfer means for introducing a calculated amount of agent into the chamber, and/or carbon dioxide control means for controlling the concentration of carbon dioxide in the chamber, and/or temperature control means for controlling the temperature in said chamber and/or mixing means for mixing the cell population and agent within the chamber and/or, timing means for timing the incubation period and/or, display means for displaying to the user the remaining time period of the incubation period and/or alarm means for altering the user of the completing of incubation and/or harvesting means for harvesting cells from the chamber and/or, removal means for removing a sample of cells and/or sealing means for sealing a storage container comprising a cellular population and/or communication means for the device to remotely communicate orders and/or confirm that operations are being or have been preformed correctly. Claims 15 and 16 embody the device of claims 3 or 4 wherein the harvesting means harvest the undifferentiated cells from the chamber. Claims 17 and 18 embody

the device of claims 3 and 4 wherein the communicating means includes a microprocessor. Claim 19 embodies the device of any one of claims 1-4 wherein the committed cells are non-cancer cells. Claim 20 embodies the device of any one of claims 1-4 wherein the committed cells are differentiated cells. Claim 21 embodies the device of any one of claims 1-4 wherein the committed cells are hematopoietic cells. Claims 22 embodies the device of any one of claims 1-4 wherein the committed cells are selected from CFC-T cells, CFC-B cells, CFC-Eosin cells, CFC-Bas cells, CFC-GM cells, CFC-MEG cells, CFC-E cells, T cells and B cells. Claim 23 embodies the device of any one of claims 1-4 wherein the undifferentiated cells are pluripotent stem cells. Claim 24 embodies the device of any one of claims 1-4 wherein the undifferentiated cells are stem cells selected from the group consisting of hematopoietic, neuronal, epithelial, mesenchymal, endodermal and embryonic stem cells. Claim 25 embodies the device of any one of claims 1-4 wherein the undifferentiated cells are characterized by one or more of the following cell surface markers: CD34+, HLA-DR-, CD38-, CD117, AC133, CD90, and/or CD45low. Claim 26 embodies the device of any one of claims 1-4 wherein the undifferentiated cells are MHC I and/or MHC II. Claim 39 embodies the device of any one of claims 1-4 wherein the cell population including committed cells is a buffy coat blood sample or is a from a buffy coat blood sample.

Claim 27 embodies the device of any of claims 2 or 4 wherein the agent engages a receptor that mediates capture, recognition or presentation of an antigen at the surface of the committed cells. Claim 28 embodies the device of claim 27 wherein the receptor is MHC I or MHC II. Claim 29 embodies the method of claim 28 wherein the class I antigen is HLA-A, HLA-B, HLA-C, HLA-E, HLA-F or an HLA-G receptor, and the class II antigen is HLA-DM, HLA-DP, HLA-DQ or HLA-DR. Claim 30 embodies the device of claim 29 wherein the receptor is HLA-DR. Claim 31 embodies the device of claim 27 wherein the receptor comprises a beta-chain having homologous regions. Claim 32 embodies the device of claim 31 wherein the receptor comprises the homologous region of the beta-chain of HLA-DR. Claim 33 embodies the device of claim 27 wherein the agent is an antibody to the receptor. Claim 34 embodies the device of claim 33 wherein the agent is a monoclonal antibody to the receptor. Claims 35 and 36 embody the devices of claims 33 and 34 wherein the antibody is selected from the group consisting of monoclonal antibody CR3/43 and monoclonal antibody TAL 1B5. Claim 37

embodies the device of any one of claims 2 or 4 wherein the agent modulates MHC gene expression. Claim 38 embodies the device of claim 37 wherein the agent modulated MHC I and/or MHC II expression.

Claim 40 is drawn to a device comprising a chamber, means for introducing into said chamber a population of cells including hematopoietic cells, means for introducing into said chamber "retrodifferentiation means", and incubation means.

Claim 41 is drawn to a device comprising a chamber, means for introducing into said chamber a population of cells including committed cells, means for introducing into said chamber "retrodifferentiation means", and incubation means.

When given the broadest reasonable interpretation, the preamble to claims 1, 2, 40 and 42 which recites the intended use of the claimed device is of no patentable weight in determining the limitations of the claim (M.P.E.P. section 2111.02)
If the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction. Pitney Bowes, Inc.v. Hewlett-Packard Co., 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165 (Fed. Cir. 1999). See also Rowe v. Dror, 112 F.3d 473, 478, 42 USPQ2d 1550, 1553 (Fed. Cir.1997)

Greunber discloses hollow fiber cartridges comprising a housing and a plurality of capillaries, and that the interior of the walls of the plurality of capillaries define a lumen extending between inflow and outflow openings , and the outside of the capillaries and the housing define an extra capillary space (ECS) where cell growth or population expansion takes place which fulfills the specific embodiment of a chamber. Greunber discloses that the housing includes one or two ports providing access from the ECS so that cells may be added or removed therefrom (column 1, lines 8-25) which fulfills the specific embodiments of claims 3, 4, 15 and 16 requiring means for cellular harvesting. Greunber discloses a device for the culturing of cells in bundles of hollow fibers, said device comprising an extracapillary connecting mechanism which includes a connecting chamber in fluid communication with the first and second primary orifices, a monitoring mechanism for monitoring the presence of oxygen gas and pH, a gas transfer mechanism for exchanging gas across a membrane separating the media from a

controlled gaseous environment within the gas transfer mechanism, and a gas delivery mechanism for delivering specific gases such as oxygen, carbon dioxide and nitrogen to the controlled gaseous environment (column 5, lines 9-20) which fulfills the specific embodiments of claims 1-4 and 11-14 regarding the "transfer means" and claims 1-4 regarding the "carbon dioxide control means". Gruenberg discloses that the monitoring mechanism for oxygen and pH combined with the controlled gas transfer mechanism provides a consistent homogeneous environment for the cells and overcomes the resistance of the capillaries to diffusion of oxygen because oxygen can be added to the inside of the ECS and does not have to diffuse from the lumen (column 7, lines 19-25). Gruenberg discloses that the harvested cells are captured in the centrifuge of the apheresis instrument and that this results in the isolation of cells in a completely closed system minimizing the risk of contamination (column 8, lines 23-26) which fulfills the specific embodiments of claims 3 and 4 regarding sealing means for sealing a storage container comprising a population of cells.

Greunber discloses that the device is automated by a computer-controlled mechanism capable of adjusting both the oxygen concentration, and pH and providing fresh growth media (column 9, lines 19-27, column 10, line 63 to column 11, line 13) which fulfills the specific embodiments of and claims 1-4 and 17-18 regarding the communicating means.. Greunber discloses an industrial scale device comprising a plurality of cartridges (column 11, lines 34-37). Greunber discloses a gas flow metering device including a heating device (column 12, line 63 to column 13, line 13) which fulfills the specific embodiments of claims 1-4 regarding an "incubator means" and a growth media reservoir heated to 37 degrees (column 12, lines 18-23). The monitoring of pH by a pH electrode further fulfills the specific embodiment of claims 17 and 18, because monitoring the pH of a cell culture medium is indicative of monitoring the cell concentration in the culture which fulfills the specific embodiment of claim 3 and 4 requiring means for conducting cell counts.

Greunber discloses the above device further comprising an apheresis instrument to harvest the cells by forcing the cells out by centrifugal force and capturing the flushing media into a waste container (column 15, lines 21-33) which also fulfills the specific embodiments of claims 1-4 and 15-16 requiring "harvesting means".

Greunber discloses that any type of cell which can grow in a cell culturing device, can be cultured or grown in the cell growing devices of the present invention (column 16, lines 8-10).

Greunberg fulfills the specific embodiments of claims 19-39 because the limitations of these claims are drawn to the intended use of the claimed device and do not serve to characterize the device over the prior art.

***Claim Rejections - 35 USC § 103***

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 1-10 and 15-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gruenberg (U.S. 5,627,070) in view of Von Behrens et al (WO 93/16384).

Claims 5 and 6 embody the device of claims 3 and 4 wherein the means for conducting cell counting is a coulter counter. Claims 7 and 8 embody the device of claims 3 and 4 wherein the means for conducting cell counting is a cytometer. Claims 9 and 10 embody the device of claims 3 and 4 wherein the means for conducting cell counting is a miniaturized coulter counter.

Gruenberg teaches the specific embodiments of claims 1-4 and 15-41 for the reasons set forth above. Gruenberg does not specifically teach inclusion of a cell counting device, such as a cytometer or a coulter counter within the device for growing cells in vitro.

Von Behrens et al teach methods of counting cells in a sample solution comprising cultured cells (page 21, lines 22-23). The methods taught by Von Behrends include measuring the electrical impedance across an orifice through which the sample solution is caused to flow, and process the number and intensity of the pulses to provide enumeration data (for example, claim 5) which fulfills the specific embodiment of "Coulter counter". Von Behrens et al also teach cell counting by means of passing a sample through a flow cell where it is intersected with

a laser bean and enumerating the number of cells by processing the light scattering data (for example claim 6) which fulfills the specific embodiments of "cytometer".

It would have been prima facie obvious at the time the claimed invention was made to include devices for cell counting by means of cytometer or Coulter counting as part of the automated tissue culture device. One of skill in the art would have been motivated to do so by the teachings of Von Behrends et al on the methods of counting cells from solutions comprising cultured cells, and because one of skill in the art would be motivated to have a totally automated cell culture device which quantifies the final number of cells, or quantifies samples intermediate to the end of the culture period in order to provide further data on the cell growth parameters of a particular batch of cells without requiring human labor.

16. Claims 1-4 and 11-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gruenberg (U.S. 5,627,070) in view of Hochman (U.S. 5,976,825).

Claims 11 and 12 embody the device of claims 3 and 4 wherein the transfer means for the agent is a syringe-driven motor. Claims 13 and 14 embody the device of claims 3 and 4 wherein the transfer means for the calculated amount of agent is a syringe-driven motor.

Gruenberg teaches the specific embodiments of claims 1-4 and 15-41 for the reasons set forth above. Gruenberg teaches a transfer means for the transference of cells wherein said transfer means is a syringe (column 8, lines 33-34). Gruenberg teaches the addition of relatively small amounts of serum, growth factors and hormones to the culture system (column 2, lines 43-48). Gruenberg does not specifically teach a motor-driven syringe as a transfer means of serum, growth factors or hormones.

Hochman teaches methods for screening candidate drugs for activity to prevent or inhibit Alzheimer's disease or CNS-based swelling comprising exposing glial cells in culture to drug candidates (column 3, line 62 to column 5, line 15). Hochman teaches that the host computer system controlling the apparatus can comprise a peripheral control board to control mechanical interfaces, such as motor driven syringes (column 14, lines 52-57).

It would have been prima facie obvious at the time the claimed invention was made to incorporate a motor driven syringe into the device of Gruenberg. One of skill in the art would have been motivated to do so by the teachings of Hochman on the incorporation of peripheral

devices into cell culture apparatuses. One of skill in the art would be motivated to do so in order to introduce relatively small amounts of serum, growth factors and hormones into the cell culture medium as needed. One of skill in the art would be motivated to have a motor driven syringe controlled by the microprocessor means in order to ensure that the cell culture was growing at an optimized rate by replenishing needed growth factors and hormones to said culture.

17. All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
9/12/2005

Karen A Canella
KAREN A. CANELLA PH.D
PRIMARY EXAMINER